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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/978,333	10/15/2001	Peter M. Glazer	YU 132 (OCR 653)	4662

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EXAMINER	
MYERS, CARLA J	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 08/11/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	Application No. 09/978,333	Applicant(s) GLAZER, PETER M.	
	Examiner Carla Myers	Art Unit 1634	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 21 July 2005 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☐ The period for reply expires _____ months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☒ The Notice of Appeal was filed on *21 July 2005*. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☒ Applicant's reply has overcome the following rejection(s): See Continuation Sheet.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *7-12 and 15-25*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because:
    see Continuation sheet.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). _____
13. ☐ Other: _____.

Continuation of 5. Applicant's reply has overcome the following rejection(s): the rejection of claims 15-24 under 35 U.S.C. 112 second paragraph (i.e., the rejection set forth on page 13 of the Office action of 5/10/2005 .

Continuation of 11. The request for reconsideration has been considered but does NOT place the application in condition for allowance. In the response of 7/21/2005, Applicants state that the rejection of the claims based on the finding that the claims are not enabling for methods in which the TFO has a Kd of more than 2 x 10-7 is moot since the claims were amended to recite that the TFO has a Kd of less than 2 x 10-7. It is acknowledged that this aspect of the rejection was rendered moot by the previous amendment to the claims. However, the rejection was maintained over the finding that while the specification is enabling for methods for in vitro and ex vivo targeted recombination using a donor tethered or unlinked to a TFO having a Kd of less than or equal to 2 x 10-7, the specification is not enabling for methods of in vivo targeted recombination. Applicants state that the declaration of Dr. Glazer filed in parent application 09/411,291 teaches that nucleic acid molecules are taken up by cells in animals such as mice without special delivery methods. However, declarations, such as those submitted under 37 CFR 1.131 and 37 CFR 1.132, filed during the prosecution of the parent application do not automatically become a part of this application. Accordingly, this declaration has not been considered. Applicants state that the amount of experimentation required to practice the claimed invention is not undue. However, as discussed in the previous Office action, the technique of in vivo triple helix therapy is highly unpredictable and the results obtained using isolated cells in vitro or ex vivo cannot be extrapolated to in vivo settings. Applicants comments regarding the ability to perform some level of experimentation and the ability to administer oligonucleotides in vivo do not address the specific issue at hand of the unpredictability surrounding the in vivo administration of triple helix forming oligonucleotides which are to be used for targeted recombination and mutagenesis. Applicants state that the specification describes the in vitro administration of TFO's and provides results in Examples 6 and 7 of the use of TFOs. Applicants thereby conclude that in vivo administration of TFOs is predictable and does not require undue experimentation. However, these assertions are not supported by any evidence or scientific arguments. The previous Office action discusses a number of references which clearly set forth the unpredictability in the art of using TFOs in vivo for recombination and targeted mutagenesis. Applicants response does not address these issues or the references. Further, the results set forth in Example 7 of the specification are not directed to the use of TFOs in vivo in combination with a donor nucleic acid. Rather, Example 7 discusses the use of the AG30 TFO alone. The present claims require targeted recombination of a nucleic acid molecule using a TFO in combination with a donor nuceic acid that recombines with a target sequence. Thereby, a showing that mice can be treated with an AG30 TFO is not sufficient to establish the predictable use of any TFO in combination with a donor nucleic acid to achieve targeted recombination in vivo. With respect to the 112, second paragraph rejection of claims 19 and 20, Applicants state that one would know that the donor nucleic acid defined in claim 7 is the same as the donor nucleic acid defined in claims 19 and 20. This argument is not persuasive because claims 19 and 20 do not specify that the donor nucleic acids are the same. While claim 7 does refer to a donor nucleic acid in general, claim 19 refers to "an exogenously supplied donor nucleic acid." Since claim 7 does not state that the donor nucleic acid is one that is exogenously supplied, it is unclear as to whether the donor nucleic acid set forth in claim 7 is the same as or distinct from "an exogenously supplied donor nucleic acid" referred to in claim 19. Similarly, while claim 7 refers to a donor nucleic acid in general, claim 20 refers to "a donor nucleic acid that is tethered to the oligonucleotide." Claim 20 does not specify that the claim intends to further define the donor nucleic acid of claim 7 as one that is tethered to the oligonucleotide. Claim 20 does not clearly set forth the relationship between the donor nucleic acid of claim 7 and the tethered donor nucleic acid. Thereby, it is unclear as to whether the donor nucleic acid referred to in claim 20 is the same as or distinct from the donor nucleic acid of claim 7 and it is unclear as to what is intended to be the relationsip between the 2 donor nucleic acids. With respect to the 102 and 103 rejections, Applicants state that Chan is not prior art to the claimed invention because the present invention is entitled to priority to 1995. Applicants state that at least column 3 of the '376 patent discloses that TFOs can be used to stimulate recombination and that TFOs are useful alone or linked to reactive moities. However, these general teachings regarding a "reactive moiety" in the '376 patent do not provide basis for the specific concept of linking a donor recombinant nucleic acid to the TFO, as is encompassed by the present claims. Applicants further state that the '376 patent defines the TFOs as being of a length of 7 to 40 nucleotides and since this length includes the range of 10 to 40 nucleotides, the present claims have priority to the '376 and '426 patents. Applicants also assert that because the '376 patent discloses TFOs of 10, 20, 30 and 57 nucleotides, that this provides basis for TFOs of 10 to 60 nucleotides. However, the teachings in the '376 and '426 patents regarding these specific lengths of TFOs do not provide basis for the concept set forth in present claim 8 of a TFO consisting of 10 to 60 nucleotides (i.e., the examples of TFOs of 10, 20, 30 and 57 nucleotides do not provide basis for a TFO of 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 58, 59, or 60 nucleotides). Additionally, the teachings in the '376 and '426 patents regarding the length of TFOs does not provide basis for the specifically claimed lengths of donor nucleic acid fragments (i.e., a donor nucleic aicd of at least 30 residues, as recited in claim 12; or a donor nucleic acid of 10 to 40 nucleotides, as recited in claim 25) since the donor nucleic acids are clearly distinct from the TFOs. Appplicants also argue that because the '376 and '426 patents discuss gene therapy and its use to treat well known disorders such as retinobalstoma, cystic fibrosis and sickle cell anemia, one would recognize that these teachings provide support for the use of TFOs to target hemoglobin, cystic fibrosis and hemophilia genes. However, the teachings in the '376 and '426 patents were limited to gene therapy. These patents do not provide basis for the concept of applying the targeted recombination method using TFOs and donor nucleic acids to treatments targeting hemoglobin, cystic fibrosis or hemophilia. Lastly, Applicants state that the '376 and '426 patents discuss targeting the xeroderma pigmentosum gene and that it was well known in the art that this gene is involved in excision repair. Thereby, Applicants conclude that the '376 and '426 patents provide basis for targeting any excision repair pathway gene. However, the teachings in the specification regarding targeting one species (i.e., the xeroderma pigmentosum gene) do not provide basis for the broader concept claimed of targeting a genus of genes (i.e., any excision repair pathway gene).

Carla Myers

CARLA J. MYERS
PRIMARY EXAMINER

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